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ORIGINAL ARTICLE

Impact of type 2 diabetes on left ventricular geometry and diastolic function in hypertensive patients with chronic kidney disease

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Left ventricular hypertrophy (LVH) and diastolic dysfunction are very common in patients with chronic kidney disease (CKD). Aim of this study was to evaluate the impact of type 2 diabetes on LV geometry and diastolic function in hypertensive patients with CKD. We enrolled 288 Caucasian subjects with hypertension and CKD; of them, 112 had diabetes. Patients with cardiovascular (CV) diseases, glomerular filtration rate (GFR) $>60\,ml\,min^{-1}$ per $1.73\,m^2$, dialysis treatment and other major non-CV diseases were excluded. All patients underwent routine biochemical analyses and echocardiographic examination with tissue Doppler imaging (TDI). Patients with diabetes had significantly higher LV wall thicknesses ($P=0.0001$), relative wall thickness (RWT) ($P=0.0001$) and left atrium volume index ($P=0.03$), when compared with patients without diabetes. Further, diabetic patients had very high prevalence of concentric LVH. Em, evaluated by TDI, was significantly lower in patients with diabetes ($P=0.005$). However, the difference lost statistical significance after correction by analysis of covariance for RWT. Multiple stepwise linear regression analysis showed that the variables independently associated with Em were: age (β 0.364; $P=0.0001$), GFR (beta 0.101; $P=0.019$), and the presence of diabetes (β 0.166; $P=0.002$). Our study showed that in hypertensive patients with CKD the presence of diabetes is associated with increased LV-wall thicknesses and concentric geometry; further, diabetes together with renal function (GFR) is associated with worse diastolic function, independently of potential confounders, such as age, gender, body mass index and blood pressure.
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Introduction

Left ventricular hypertrophy (LVH), a frequent expression of subclinical target-organ damage related to hypertension, is a very common structural abnormality in patients with chronic kidney disease (CKD),[1–3] and is independently associated with cardiovascular (CV) morbidity and mortality.[4,5] LV diastolic dysfunction is also frequent among CKD patients and is associated with the risk to develop heart failure and with mortality.[6–8]

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Diabetes, often together with hypertension, represents today the most common cause of CKD.[9] The negative impact of diabetes on CV prognosis is well established.[10,11] Particularly, diabetes is associated with coronary artery disease and with LV diastolic dysfunction.[12,13]

A recent paper by our group[1] confirmed that the prevalence of LVH is very high in hypertensive patients with CKD, and is increasingly greater along with declining renal function. Moreover, in hypertensive patients with CKD, LVH is often characterized by the simultaneous increase of LV-wall thicknesses, internal diameters, relative wall thickness (RWT), and diastolic function is worse in comparison with hypertensive patients with normal renal function.[1]

In the present study we evaluate the impact of type 2 diabetes on LV hypertrophy, geometry and diastolic function in a group of hypertensive patients with CKD.

Patients and methods

The study was carried out in accordance with the Declaration of Helsinki and institutional guidelines; enrolled subjects were aware of the investigational nature of the study and agreed to participate after informed consent.

Study population

The patients were selected among the subjects consecutively attending our Internal Medicine, Nephrology and Hypertension Unit. All subjects underwent a detailed review of their medical history and routine laboratory measurements.

Patients having hypertension and CKD, with or without diabetes, were eligible for this study.

The definition of hypertension was based on the 2007 European Society of Hypertension/European Society of Cardiology Guidelines.[14] Clinic blood pressure (BP) was considered as the average of three consecutive measurements using a mercury sphygmomanometer after the subjects had been supine for 5 min.

Patients were defined diabetics when fasting serum glucose level was $\geqslant$126 mg per 100 ml and/or plasma glucose 2 h after 75 g glucose load was $\geqslant$200 mg per 100 ml,[15] they had a previous diagnosis of diabetes or they were currently using any diabetes drug.

CKD was defined and stratified using the National Kidney Foundation—Kidney Disease Outcome Quality Initiative (K/DOQI) classification:[16] stage 1 (kidney damage with normal or increased glomerular filtration rate (GFR)): GFR $\geqslant$90 ml min^{-1} per 1.73 m^2; stage 2 (mild CKD): GFR 89–60 ml min^{-1} per 1.73 m^2; stage 3 (moderate CKD): GFR 59–30 ml min^{-1} per 1.73 m^2; stage 4 (severe CKD): GFR 29–15 ml min^{-1} per 1.73 m^2; and stage 5 (kidney failure): GFR $<$15 ml min^{-1} per 1.73 m^2.

Patients on stage 1 and 2 CKD or on dialysis treatment were excluded from the study.

GFR was estimated by Cockcroft and Gault equation[17] corrected by body surface area. This method was used for the selection and classification of patients. In the enrolled subjects GFR was also estimated by simplified modification of diet in renal disease (MDRD) Study equation:[18] 186 $\times$ serum creatinine (mg per 100 ml)$^{-1.154}$ $\times$ age (years)$^{-0.203}$ ($\times$ 0.742, if female). The ethnicity factor ($\times$ 1.21, if black) of the equation was not used because all the subjects enrolled in our study were Caucasian. We chose to control our results by MDRD equation to minimize a possible bias deriving from the method chosen to estimate GFR.

The following exclusion criteria were applied: age $<$20 or $>$75 years, history of CV diseases (previous coronary artery disease, history of angina or myocardial infarction, abnormalities of cardiac rhythm, heart failure, ejection fraction (EF) $<$55%, moderate or severe valvular diseases, previous transient ischaemic attack or stroke), GFR $>$60 ml min^{-1} per 1.73 m^2, current or previous dialysis treatment, previous renal transplantation, other major non-CV diseases. Coronary artery disease was also ruled out, excluding patients having regional wall motion abnormalities on echocardiographic examination.

After the application of the exclusion criteria, a total of 288 Caucasian subjects with hypertension and CKD were included in the study. Out of the 288 patients, 112 had type 2 diabetes and 176 had not.

Laboratory methods

Determination of routine biochemical parameters was performed with standard techniques by using an autoanalyser (Boehringer Mannheim for Hitachi system 911, Mannheim, Germany).

Echocardiographic methods

The echocardiographic examination was performed using an Acuson Sequoia 512 system (Siemens, Mountain View, CA, USA). Images were taken in left lateral decubitus position. Two-dimensional targeted M-mode echocardiography was performed using the parasternal long-axis acoustic window to evaluate left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter, interventricular septum thickness and posterior wall thickness (PWT) according to the American Society of Echocardiography recommendations.[19] Left atrial diameter was also determined, and left atrial volume indexed by body surface area (LAVI) was calculated by the biplane Simpson's method.[20]

Only those frames with optimal visualization of interfaces and showing simultaneous visualization of septum, left ventricular diameters and posterior wall were used for readings.

Left ventricular mass (LVM) was determined using the American Society of Echocardiography-corrected cube formula[21] and was indexed by both body surface area (LVMI) and height elevated by a power of 2.7 (LVMH$^{2.7}$) in order to provide a more stringent allowance for overweight.[22] In our laboratory, the mean intra-observer variability for LVM was 8.6%.

LVH was defined as LVM indexed by body surface area (LVMI) $>$125 g m^{-2} in men and $>$110 g m^{-2} in women, as suggested by the 2007 European Society of Hypertension/European Society of Cardiology Guidelines.[14] RWT was calculated as the ratio of 2PWT/LVEDD. Concentric LVH was defined as LVMI $>$125 g m^{-2} in men and $>$110 g m^{-2} in women, with RWT $>$0.45; eccentric LVH was defined as LVMI $>$125 g m^{-2} in men and $>$110 g m^{-2} in women, with RWT $<$0.45.

Left ventricular EF was assessed by 2D-echo using modified Simpson's rule.[23]

Diastolic function was evaluated using both mitral inflow and tissue-Doppler echocardiography, performed according to the American Society of

Echocardiography recommendations.[24] Mitral inflow was assessed in the apical four-chamber view, using pulsed-wave Doppler echocardiography, with the Doppler beam aligned parallel to the direction of flow and the sample volume at the leaflet tips. From the mitral inflow profile, the E-wave (E) and A-wave (A) peak velocities, E/A ratio and E-deceleration time were measured. Isovolumic relaxation time was calculated between aortic valve closure and the start of E-wave.

Tissue Doppler imaging (TDI) of the mitral annulus was obtained from the apical four-chamber view, using a 1- to 2-mm sample volume placed in the lateral mitral valve annulus, to evaluate early diastolic myocardial velocity (Em) and atrial diastolic myocardial velocity (Am). The E/Em ratio was also calculated.

We decided to evaluate diastolic function principally by means of TDI, as parameters measured by TDI are more preload-independent than those measured by mitral inflow;[25] further, Em is inversely related to myocardial fibrosis.[25] E/Em is considered as a good predictor of elevated LV filling pressure.[26]

Echocardiographic data are expressed as the average of five consecutive cardiac cycles. Images were read by a single cardiologist, who was blinded to the patient's clinical characteristics.

Statistics

Data for continuous variables are given as mean ± standard deviation.

Differences between groups were evaluated, when appropriate, using analysis of variance and the independent-sample Student's *t*-test with Bonferroni correction, for continuous variables and the χ^2-test, with Yates' correction, for the categorical variables. When appropriate, differences were adjusted, by analysis of covariance (ANCOVA), for body mass index (BMI).

Univariate associations between the variables were assessed by the Pearson's correlation coefficients and multiple stepwise linear regression analysis. This latter was performed in the whole group of 288 patients considering Em as the dependent variable, and including in the statistical model age, sex, BMI, systolic and diastolic BP, GFR, haemoglobin, LAVI and type 2 diabetes (this latter included as a dichotomous variable). Multiple regression analysis was also repeated adding RWT to the model, and replacing GFR with serum creatinine and replacing GFR estimated by Cockcroft and Gault equation with GFR estimated by MDRD equation.

The null hypothesis was rejected at a two-tailed $P \leqslant 0.05$.

The statistical analyses were performed using the SYSTAT DATA software package, version 5.2 (Systat, Evanston, IL, USA).

Results

The main demographic and clinical data of the patients are synthesized in Table 1. There were no significant differences in age, distribution of sex, GFR, haemoglobin, systolic and diastolic BP, pulse pressure and known duration of both hypertension and CKD. BMI was higher in patients with type 2 diabetes ($P = 0.036$).

All patients received pharmacological treatment. Anti-hypertensive treatment for the patients with type 2 diabetes was as follows: 30% ACE inhibitors (alone or in combination with a diuretic); 33% AT1 blockers (alone and in combination with a diuretic); 5% β-blockers or α-β-blockers; 1% α-blockers; 10% calcium-channel blockers; 2% diuretic alone; 19% a combination of two or more of these drugs. Use of the different classes of anti-hypertensive drugs was not different in comparison with patients without diabetes ($P = 0.93$).

Around 22% of the whole sample was on current recombinant human erythropoietin treatment. In the group of patients with type 2 diabetes, 67% received

Table 1 Principal demographic and clinical data (mean ± s.d.) of 112 hypertensive patients with chronic kidney disease and with type 2 diabetes, and of 176 hypertensive patients with chronic kidney disease and without diabetes

	Type 2 diabetic patients (N = *112*)	*Non-diabetic patients* (N = *176*)	P
Age, years	63.2 ± 8.4	62.9 ± 13.7	0.852
Males/females	70/42	109/67	0.982
Body mass index, kg m^{-2}	27.6 ± 3.7	26.7 ± 3.8	0.036
Serum creatinine, μmol l^{-1}	254.6 ± 125.5	298.8 ± 185.6	0.029
GFR_{C-G}, ml min^{-1} per 1.73 m^2	29.2 ± 12.35	27.9 ± 15.1	0.435
GFR_{MDRD}, ml min^{-1} per 1.73 m^2	25.8 ± 11.9	25.9 ± 16.2	0.969
Haemoglobin, g l^{-1}	126 ± 12	125 ± 14	0.375
Systolic blood pressure, mm Hg	146 ± 19	143.2 ± 19	0.212
Diastolic blood pressure, mm Hg	80.2 ± 11.9	80.8 ± 13.7	0.687
Pulse pressure, mm Hg	65.9 ± 16.4	62.4 ± 18.6	0.104
Known duration of hypertension, years	12.1 ± 9.3	11.8 ± 8.5	0.779
Known duration of chronic kidney disease, years	2.95 ± 3.5	3.8 ± 5.3	0.134

Abbreviations: GFR_{C-G}, glomerular filtration rate estimated by Cockcroft–Gault equation; GFR_{MDRD}, glomerular filtration rate estimated by MDRD equation.

insulin therapy, and mean value of HbA1c was 7.3%.

Table 2 shows the main echocardiographic findings. Patients with type 2 diabetes had significantly higher interventricular septum thickness, PWT ($P=0.0001$ for both), left atrium diameter ($P=0.014$) and LAVI ($P=0.03$) when compared with patients without diabetes. Further, RWT was significantly higher in patients with type 2 diabetes, also after correction by ANCOVA for BMI (Table 2). LVEDD, left ventricular end-systolic diameter and EF were not significantly different comparing the two groups. LVMI and $LVMH^{2.7}$ were slightly higher in patients with type 2 diabetes, but the difference did not reach statistical significance.

In regard to diastolic function, parameters evaluated by mitral inflow (E/A, deceleration time and isovolumic relaxation time) were not significantly different comparing patients with and without type 2 diabetes (Table 2). TDI showed that Em was significantly lower in patients with type 2 diabetes, also after correction by ANCOVA for BMI or for LAVI. When we adjusted by ANCOVA for RWT, the difference lost statistical significance (Table 2); thus, the differences in Em values were largely explained by the higher RWT of patients with type 2 diabetes. Further, in diabetic patients a highly significant inverse correlation between Em and RWT was found (Figure 1); Em was also inversely correlated with LAVI ($r=-0.188$; $P<0.01$).

Moreover, the ratio E/Em was significantly higher in patients with type 2 diabetes ($P=0.001$).

We further analyzed the grading of diastolic dysfunction[20] in patients with and without diabetes. Overall, the prevalence of diastolic dysfunction was significantly higher in patients with type 2 diabetes (100/112 (89.3%)) than in those without diabetes (129/176 (73.3%)) ($P=0.002$). The prevalence of the different grades of diastolic dysfunction is shown in Table 3. Of note, only a minority of patients had diastolic dysfunction grade III or IV; this can be chiefly explained bearing in mind that all the patients with heart failure were excluded from the study. However, a slightly higher (although not significant) prevalence of more advanced grades of diastolic dysfunction was found in patients with type 2 diabetes (Table 3); the slightly higher prevalence of diastolic dysfunction grade II and III may also contribute to explain why there was no significant difference of mitral inflow measurements

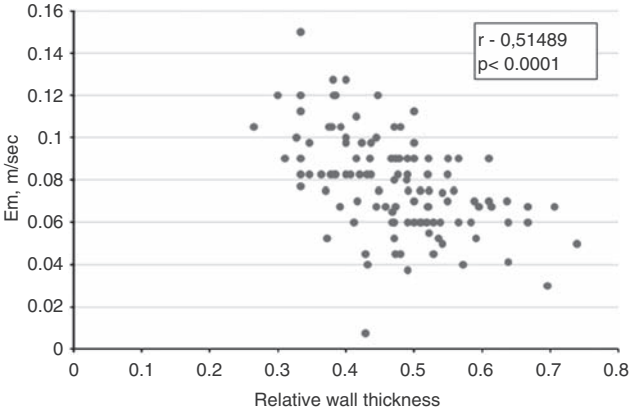

Figure 1 Univariate correlation between early diastolic myocardial velocity (Em) and relative wall thickness (RWT) in 112 hypertensive patients with chronic kidney disease and type 2 diabetes.

Table 2 Echocardiographic data (mean ± s.d.) of 112 hypertensive patients with chronic kidney disease and with type 2 diabetes, and of 176 hypertensive patients with chronic kidney disease and without diabetes

	Type 2 diabetic patients (N = *112*)	*Non-diabetic patients* (N = *176*)	P
Left ventricular end-diastolic diameter, mm	50.69 ± 5.5	51.7 ± 5.56	0.140
Left ventricular end-systolic diameter, mm	32.15 ± 5	33 ± 5.04	0.153
Ejection fraction, %	66.19 ± 5.1	65.43 ± 5.5	0.243
Interventricular septum thickness, mm	12.27 ± 2.1	11.42 ± 1.86	0.0001
Posterior wall thickness, mm	11.84 ± 2.05	10.97 ± 1.85	0.0001
LVMI, $g\,m^{-2}$	137.3 ± 40.4	130.8 ± 42.3	0.197
$LVMH^{2.7}$, $g\,m^{-2.7}$	65.9 ± 21	61.6 ± 20.5	0.081
Relative wall thickness	0.472 ± 0.09	0.426 ± 0.07	0.0001*
Left atrium diameter, mm	39.2 ± 5.5	37.5 ± 5.9	0.014
LAVI, $ml\,m^{-2}$	36.2 ± 16	31.8 ± 18	0.03
E/A	0.795 ± 0.36	0.814 ± 0.3	0.629
DT, $m\,s^{-1}$	310.5 ± 90	304.4 ± 85	0.537
IVRT, $m\,s^{-1}$	114 ± 24.4	117 ± 24.5	0.302
Em, $m\,s^{-1}$	0.078 ± 0.023	0.087 ± 0.028	0.005†, #, ‡
E/Em	9.65 ± 5.53	7.9 ± 3.32	0.001

Abbreviations: A, A-wave peak velocity; ANCOVA, analysis of covariance; DT, E-wave deceleration time; E, E-wave peak velocity; Em, early diastolic myocardial velocity; IVRT, isovolumic relaxation time; LAVI, left atrial volume indexed by body surface area; $LVMH^{2.7}$, left ventricular mass indexed by $height^{2.7}$; LVMI, left ventricular mass indexed by body surface.
*$P=0.0001$ also after adjustment by ANCOVA for body mass index.
†$P=0.013$ after adjustment by ANCOVA for body mass index.
#$P=0.01$ after adjustment by ANCOVA for LAVI.
‡$P=0.28$ after adjustment by ANCOVA for relative wall thickness.

Table 3 Prevalence of different grades of diastolic dysfunction in 112 hypertensive patients with chronic kidney disease and with type 2 diabetes, and in 176 hypertensive patients with chronic kidney disease and without diabetes

	Type 2 diabetic patients (N = 112)	*Non-diabetic patients (N = 176)*
Prevalence of diastolic dysfunction, *n* (%)	100/112 (89.3)	129/176 (73.3)*
Grade I, *n* (%)	85/100 (85)	121/129 (93.8)
Grade II, *n* (%)	9/100 (9)	6/129 (4.65)
Grade III, *n* (%)	6/100 (6)	2/129 (1.55)
Grade IV, *n* (%)	0/100 (0)	0/129 (0)

*$P = 0.002$ ($P = 0.108$ comparing the prevalence of the grades of diastolic dysfunction between patients with and without diabetes).

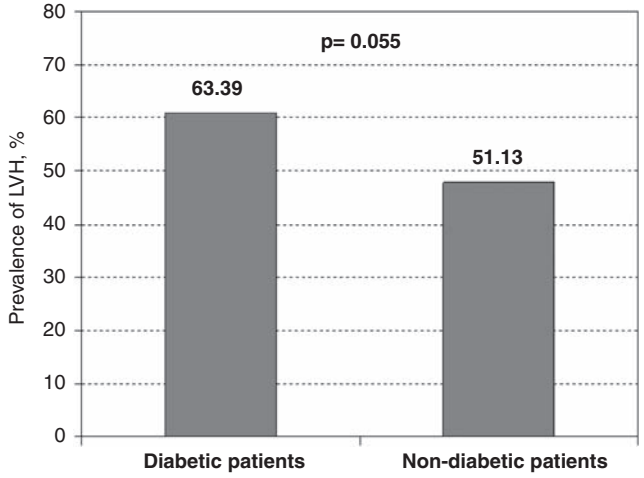

Figure 2 Prevalence of left ventricular hypertrophy in hypertensive patients with chronic kidney disease, with and without type 2 diabetes.

comparing patients with and without diabetes (Table 2).

As shown in Figure 2, the prevalence of LVH was 63.39% ($N = 71/112$) in patients with type 2 diabetes and 51.13% ($N = 90/176$) in those without diabetes, but the difference was only of borderline significance ($P = 0.055$).

The distribution of concentric and eccentric patterns of LVH was significantly different comparing patients with and without diabetes ($P < 0.0001$—Figure 3), as diabetic patients had a very high prevalence of concentric LVH (73.23%).

The multiple stepwise linear regression analysis, performed considering Em as the dependent variable, and including in the statistical model age, sex, BMI, systolic and diastolic BP, GFR (estimated by Cockroft-Gault equation corrected by body surface area), haemoglobin, LAVI and type 2 diabetes (included as dichotomous variable), showed that the variables independently associated with Em were: age ($\beta = 0.364$; $P = 0.0001$), GFR ($\beta = 0.101$; $P = 0.019$) and the presence of diabetes ($\beta = 0.166$; $P = 0.002$) (Table 4). Further, when we added RWT

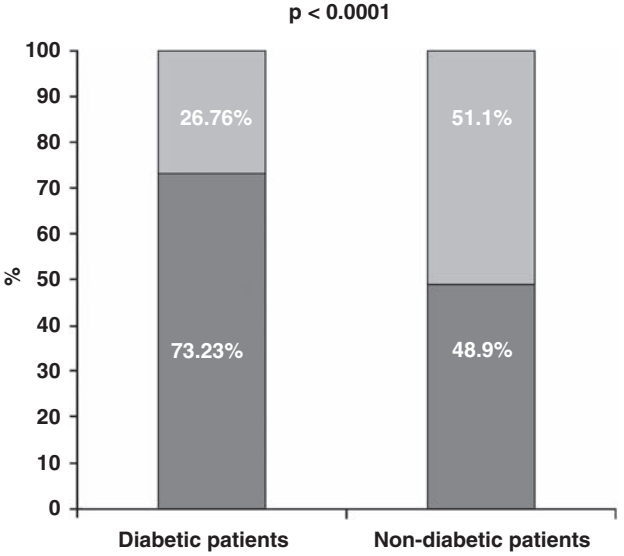

Figure 3 Prevalence of concentric and eccentric patterns of left ventricular hypertrophy in hypertensive patients with chronic kidney disease, with and without type 2 diabetes. Dark grey-concentric LVH; light grey = eccentric LVH.

Table 4 Multivariate correlates of early diastolic myocardial velocity in the whole study population of 288 hypertensive patients with chronic kidney disease

	Regression coefficient	*Standard error*	*Standard regression coefficient (beta)*	P
Age	−0.00008	0.00001	−0.364	0.0001
GFR	0.00029	0.00012	0.101	0.019
Diabetes	−0.00888	0.00286	0.166	0.002

Abbreviations: Em, early diastolic myocardial velocity; GFR, glomerular filtration rate estimated by Cockcroft–Gault equation corrected by body surface area.
Besides the variables listed in the table, the other covariates were sex, body mass index, systolic and diastolic blood pressure, haemoglobin and left atrial volume indexed by body surface area. When relative wall thickness (RWT) was added to the multivariate model, an independent inverse relationship between RWT and Em was found ($\beta = 0.340$; $P = 0.0001$), and the relationship between diabetes and Em lost statistical significance ($P = 0.146$). The inclusion into the model of serum creatinine or GFR estimated by MDRD equation, instead of GFR estimated by Cockroft–Gault equation, did not significantly change the results.

to the multivariate model, an independent inverse relationship between RWT and Em was found (β 0.340; $P = 0.0001$), and the relationship between diabetes and Em lost statistical significance ($P = 0.146$).

Similar results were obtained when GFR estimated by Cockroft–Gault equation was replaced, respectively, by GFR estimated by MDRD equation or by serum creatinine (data not shown).

Discussion

In this study we evaluated the impact of type 2 diabetes on LV structure and diastolic function in a

group of hypertensive patients with CKD. Patients with and without diabetes were not different in regard to several clinical characteristics, including BP, GFR, duration of hypertension and of CKD.

The main findings of our study are the following:

(1) type 2 diabetes is associated with increased LV-wall thicknesses and concentric geometry;
(2) type 2 diabetes, together with renal function (GFR), is associated with worse diastolic function independently of potential confounders, such as age, sex, BMI and BP.

In hypertensive patients, concomitant diabetes has been associated with higher LVM, more concentric geometry and impaired systolic and diastolic function.[27,28] Moreover, diabetes has a negative impact on treatment-induced changes in LV structure and function in hypertensives with LVH.[29]

In the Strong Heart Study,[27] which involved a wide group of American Indians, diabetic subjects had higher LVM, interventricular septum thickness, PWT and RWT in comparison with subjects without diabetes, with no difference in LV chamber size. Similar results were obtained in the HYperGEN Study,[28] in which diabetic hypertensives had higher LVM and more concentric geometry when compared with non-diabetic hypertensives (again in this study diabetics had higher LVM, interventricular septum thickness, PWT and RWT but there was no difference with regard to LV diameter). However, in this study the relation of diabetes with LVH lost statistical significance when duration of hypertension was included in the statistical analysis.[28] In regard to LV geometry, our results are consistent with those by the Strong Heart Study[27] and the HYperGEN Study.[28] In fact, in our study, patients with diabetes had higher LV wall thicknesses (but not diameters), higher RWT and higher prevalence of concentric LVH when compared with patients without diabetes (Table 2, Figure 3). Although we observed a trend toward higher values of LVMI and $LVMH^{2.7}$, and higher prevalence of LVH in diabetic patients, these differences did not reach statistical significance. We cannot exclude that the relative small sample size could influence these findings. Further, diabetic patients had higher LV wall thicknesses, but LVEDD, although the difference was not significant, was slightly lower in comparison with patients without diabetes. As the value of LVEDD is part of the formula to calculate LVM, this may explain why the differences of LVMI, $LVMH^{2.7}$ and LVH prevalence did not reach statistical significance between the two groups.

Scant information is available in the literature about the influence of diabetes on LV structure and function in patients with CKD.

A study by Miyazato *et al*.[8] focused this issue in a sample of 67 patients with CKD (34 of whom had diabetes) and in 134 essential hypertensives with normal renal function (67 diabetics). In this study LVH was associated mainly with CKD, with no further influence of diabetes. In contrast, diastolic dysfunction (defined in this study as decreased E/A and prolonged deceleration time) was promoted by both CKD and diabetes, and the impact of diabetes appeared somewhat stronger than that of CKD.[8] Our study, in agreement with our previous results,[1,7] confirms that renal function is associated with impaired diastolic function and is independently related with Em, a parameter that has been demonstrated to be inversely related to the degree of fibrosis in ischemic, as well as in normal myocardial segments.[24] Moreover, in our study, also type 2 diabetes was independently associated with Em, and patients with diabetes had significantly lower Em values in comparison with non-diabetic patients. However, after correction by ANCOVA for RWT, this difference disappeared, showing that the negative impact of type 2 diabetes on diastole was largely explained by the association with increased RWT and concentric geometry. This was further confirmed when we added RWT to the multivariate model: the relationship between diabetes and Em lost statistical significance, highlighting an independent inverse relationship between RWT and Em.

Further, patients with type 2 diabetes had higher left atrium diameter, higher LAVI, higher E/Em ratio and higher prevalence of diastolic dysfunction when compared with patients without diabetes (Tables 2 and 3). Left atrium size, expressed in clinical practice as LAVI, is considered as a morphological expression of diastolic dysfunction, and as a marker of chronicity of increased LV filling pressure.[20] It has been demonstrated that the index E/Em has a good correlation with LV filling pressure, and this correlation has been reported to be higher in comparison with any other Doppler parameters, especially when systolic function (EF) is preserved.[25,26] In this regard, it is to note that all the patients here studied had normal EF. The mean value of E/Em in the subgroup with diabetes was 9.65, near to the cut-off value of 10, which is considered a good single predictor of elevated LV filling pressure.[25,26] Taken together, the results of our study suggest that in hypertensive patients with CKD and type 2 diabetes the impairment of diastolic function, accompanied by left atrium enlargement and increase of LV filling pressure, can be due to the development of concentric geometry with increased myocardial fibrosis.

Autopsy studies have shown increased myocardial fibrosis in patients with hypertension and diabetes,[30] as well as in patients with renal failure.[31,32] Experimental studies suggest that increased advanced glycation end-product formation associated with hyperglycaemia may be linked with increased myocardial stiffening and dysfunction.[33,34] Increased myocardial fibrosis presumably contributes to myocardial ischaemia due to the reduction in capillary density and coronary reserve.[32] Recently, even subclinical renal damage has been associated with impaired coronary flow reserve.[35] Further,

increased myocardial fibrosis has a central role in the alterations of diastolic function.

Study limitations

Our study had a cross-sectional design, so it does not allow us to draw causal relationships. Further, our study population consisted of a relatively small sample of only Caucasian subjects. This limits the applicability of our results to other racial or ethnic groups, but it is noteworthy that results similar to ours were obtained in American Indians participating to the Strong Heart Study.[27] We evaluated only clinic BP, whereas 24-h ambulatory BP was not assessed, and associations between echocardiographic variables and arterial stiffness or albuminuria were not tested, because these data were available only for a minority of patients. Lastly, as all our patients received anti-hypertensive drugs, we have to acknowledge the possible influence of the pharmacological treatment on our results. In this regard, use of the different classes of anti-hypertensive drugs was not different in patients with and without diabetes.

Conclusions

In summary, our study highlights that hypertensive patients with type 2 diabetes and CKD are characterized by impaired LV diastolic function, which is largely explained by the increase of LV wall thicknesses and by the development of concentric LVH.

These results, which are in agreement with previous findings in diabetic hypertensive patients,[27,28] may suggest that an echocardiographic examination should routinely be performed in patients having hypertension together with type 2 diabetes and CKD. Indeed, even if the patients of our sample were all free of CV diseases and heart failure, and even if renal dysfunction was not extremely advanced, there was high probability to detect LV changes.

What is known about this topic

- Left ventricular hypertrophy, frequent expression of subclinical target-organ damage related to hypertension, is a very common structural abnormality in patients with chronic kidney disease.
- In hypertensive patients, concomitant diabetes has been associated with higher left ventricular mass, more concentric geometry and impaired systolic and diastolic function.

What this study adds

- In hypertensive patients with chronic kidney disease, free of cardiovascular diseases, the presence of type 2 diabetes is associated with increased left ventricular wall thicknesses and concentric geometry.
- Type 2 diabetes, together with renal function, is associated with worse diastolic function independently of potential confounders, such as age, sex, body mass index and blood pressure.
- The negative impact of type 2 diabetes on diastole seems to be largely explained by the association with increased relative wall thickness and concentric geometry.

Conflict of interest

The authors declare no conflict of interest.

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